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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/305,084	05/04/1999	Robert J. Schneider	5914-080-999	1583

20583 7590 07/16/2007

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
07/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/305,084	SCHNEIDER ET AL	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 43-59 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 43-59 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 4/20/2007.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 43-59 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claim 43 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the selective antagonization of the ETB receptor in a patient having melanoma comprising the administration of known peptide antagonists of ET(B) receptor and antibodies which antagonize the ET(B) receptor, does not reasonably provide enablement for selectively antagonizing the ET(B) receptor by means involving the administration of anti-sense nucleic acid targeting endothelin B. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following reasons of record were set forth on page 5-7 of the Office action of March 15, 2004.

As drawn to the treatment of cancers by anti-sense therapy

The claims are drawn in part to a method of inhibiting cancer comprising the administration of an ETB antisense molecule. The specification contemplates this application as gene therapy (section 5.3, pages 26-27). The specification does not reasonably provide enablement for the administration of an ETB antisense molecule or a ribozyme targeting the ETB receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and us the invention commensurate in scope with these claims.

In order to practice the full scope of the claims, the medical procedure of gene therapy must be enabled. However, the state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene

therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), . Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of

the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claim 26 to the extent that it reads on gene therapy.

Applicant argues that the above rejection is not applicable to the claimed invention. this is not persuasive. when given the broadest reasonable interpretation, "selectively antagonizing the endothelin B receptor in said patient" includes the administration of agents which antagonize the receptor function by decreasing the level of the receptor as in the contemplated anti-sense therapy. It is noted that claim 44 embodies the method of claim 43 wherein the receptor is antagonized by administration of a receptor antagonist. If the scope of claim 43 were limited to the administration of receptor antagonists, then claim 44 would not further limit the independent claim 43. thus it appears that claim 43 is larger in scope than claim 44 and encompasses methods of antagonizing the receptor other than the administration of receptor antagonists.

Applicant argues that if one use of the claimed invention is enabled then the claims are patentable. This is not correct. Applicant is referring to the enablement requirement of product claims. Method claims must not encompass inoperative embodiments that are not clearly identified by the specification. In the instant case, the claimed method encompasses antagonism of the endothelin B receptor by anti-sense therapy.

The rejection of claims 43-46, 50, 53 and 56-59 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739, reference of the IDS filed February 8, 2001) in view of Vournakis et al (U.S. 6,063,911, cited in a previous Office action) is withdrawn in light of applicants Declaration under 37 C.R.F. 1.131

The rejection of claims 43-46, 48, 50, 53 and 56-59 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) is maintained for reasons of record.

Kikuchi et al teach that contacting of BQ-788, a ETB antagonist with a primary melanoma cell line , PM-WK, which expresses high level of ETB receptors resulted in a significant decrease in the mitogenic activity stimulated by the ET-1 or ET-3 , but that contacting with BQ-123 had no such effect (page 735, line 1 to page 746, line 2). Kikuchi et al teach that the ETB receptor subtype mainly initiates mitogenic signaling in primary melanoma (page 738, lines 6-8).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer BQ-788 to a patient having a primary melanoma expressing the ETB receptor, or a recurrent melanoma expressing the ETB receptor. One of skill in the art would have been motivated to do so by the teachings of Kikuchi et al on the ability of BQ-788 to inhibit the growth of melanoma cells expressing the ETB receptor in the presence of ET-1 and ET-3 and the teachings of Nelson et al on the ability of BQ788 to bind to ETB receptors when administered in vivo. One of skill in the art would reasonably conclude that BQ788 would bind and antagonize the ETB receptor on primary or recurrent melanoma cells in vivo even in the presence of the endogenous ET-1 and ET-3 ligands. Claims 58 and 59 are included with this rejection because they are product by process claims for the characterization of the ET(b) antagonists. The structure and properties of BQ 788 fulfill the specific embodiments of claims 58 and 59.

Applicant again argues that Kikuchi et al teaches that metastatic cell lines show down regulation of ETB and hence do not respond to ET-1 treatment. This has been considered but not found persuasive. The instant claims are drawn to the treatment of melanoma. As such, efficacy of said treatment would be recognized by one of skill in the art to include decreasing tumor burden of the primary tumor, or causing disease stabilization of the primary tumor, and/or decreasing t invasiveness of the primary tumor, which is separate from inhibiting metastatic lesions. The claims do not require that the treatment be involved in pre-metastatic events because melanoma spreads by local invasion as well as by metastasis. One of skill in the art would conclude that

deprivation of a mitogen would result in less mitosis in the primary lesion and a decrease in potential for local invasion.

Applicant argues that a skilled artisan would not have thought it desirable to treat metastatic melanoma with BQ-788. As stated above, efficacy of said treatment would be recognized by one of skill in the art to include decreasing tumor burden of the primary tumor, or causing disease stabilization of the primary tumor, and/or decreasing t invasiveness of the primary tumor, which is separate from inhibiting metastatic lesions.

Applicant argues that Kikuchi's remarks that the ETB receptor might be necessary in tumor evolution cannot be interpreted as an incentive to treat the early stages of melanoma with BQ-788. This has been considered but not found to be persuasive. Applicant is refereed to Table 1 of Kikuchi et al wherein it is shown that primary or recurrent melanoma express the ETB receptor.

Applicant argues that because Kikuchi does not teach every element of the claimed invention, the rejection cannot stand. Applicant is reminded that if Kikuchi did teach every element of the claimed invention, the rejection would be under 37 CRF 102, no 37 CRF 103

The rejection of claims 43-46, 48, 50-59 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) as applied to claims 43-46, 48, 50, 53 and 56-59 above, and further in view of Battistini et al (Pulmonary Pharmacology and Therapeutics, 1998, Vol. 11, pp. 97-112, reference of the IDS submitted July 25, 2003) is maintained for reasons of record.

Claims 51, 52, 54 and 55 specify the endothelin B antagonists of IRL-1038 and RES-701-1. Battistini et al teach that IRL-1038 and RES-701-1. as well as BQ 788 (page 100, Table 1). It would have been prima facie obvious at the time the claimed invention was made to substitute IRL-1038 or RES-701-1 for the BQ 788 taught by Kikuchi et al. One of skill in the art would have been motivated to do so by the teachings of Kikuchi that the ETB receptor subtype mainly initiates mitogenic signaling in primary melanoma and the example wherein BQ 788 counteracts a mitogenic signal. One of skill in the art would understand that other ET(B) receptor antagonists in addition to BQ 788 would precipitate the same effect on primary melanoma.. Claims 58 and 59 are included with this rejection because they are product by process claims for

the characterization of the ET(b) antagonists. The structure and properties of IRL-1038, RES-701-1, and BQ 788 fulfill the specific embodiments of claims 58 and 59.

The rejection of claims 43-50, 53 and 56-59 under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739) as applied to claims 43-46, 48, 50, 53 and 56-59 above, and further in view of Ferrara et al (U.S. 5,573,762) is maintained for reasons of record..

Ferrara et al teach that blockers of the endothelin B receptor includes antibodies (column 6, lines 15-17).

It would have been prima facie obvious at the time the claimed invention was made to substitute an anti-endothelin B antagonistic antibody for the BQ 788 taught by Kikuchi et al. One of skill in the art would have been motivated to do so by the teachings of Ferrara et al who suggest that antibodies can be used to block the endothelin B receptor and by the teachings of Kikuchi that the ETB receptor subtype mainly initiates mitogenic signaling in primary melanoma and the example wherein BQ 788 counteracts a mitogenic signal. One of skill in the art would understand that other ET(B) receptor antagonists in addition to BQ 788 would precipitate the same effect on primary melanoma.. Claims 58 and 59 are included with this rejection because they are product by process claims for the characterization of the ET(b) antagonists. The structure of an antagonistic endothelin B antibody fulfills the specific embodiments of claims 58 and 59.

Applicant teaches that neither of Battistini et al and Ferrara do no cure the deficiency of Kikuchi et al. This has been considered but not found persuasive, because Kikuchi et al provides ample motivation for the claims invention.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner,
Art Unit 1643